NEURAL CONTROL OF THE RELEASE AND ACTION OF SECRETIN

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The release and physiological actions of secretin on pancreatic exocrine secretion and gastric secretion of acid and motility are regulated by neuro-hormonal control. The release of secretin by duodenal acidification is mediated by a secretin releasing peptide (SRP). The release and action of SRP are neurally mediated depending on vagal afferent pathway. SRP activity in acid perfusate of the duodenum was substantially decreased when rats were treated with tetradotoxin (TTX), perivagal application of capsaicin, a β-adrenergic blocker, Met-enkephalin (MEK) or vagotomy. The release of secretin by SRP was abolished in rats treated with TTX, mucosal or perivagal application of capsaicin, MEK or vagotomy. Both release of secretin and pancreatic exocrine secretion (PES) elicited by duodenal acidification were also inhibited dose-dependently by Met-enkephalin, 5-HT₂ antagonist, ketanserin and 5-HT₃ antagonist, ondansetron. Stimulation of PES and inhibition of gastric acid secretion and motility by secretin in a physiological dose are also dependent on the vagal afferent pathway as these effects of secretin are abolished by perivagal capsaicin treatment or vagotomy. In conscious rats, vagotomy, vagal ligation, or perivagal colchicine but not capsaicin treatment reduced the number of secretin binding sites in the forestomach suggesting another mode of neural regulation that affects gastric motility. Except in the rat, stimulation of PES by secretin in a physiological dose is profoundly inhibited by atropine indicating the importance of a cholinergic input. In isolated and perfused rat pancreas, electrical field stimulation potentiated secretin-stimulated PES that was suppressed by atropine and anti-GRP serum, suggesting the roles of intrapancreatic cholinergic and GRP-containing neurons. In rats, secretin-stimulated PES was inhibited by a NO synthase inhibitor suggesting mediation by NO. However, the neuropeptides and neurotransmitters involved in regulation of the release and action of secretin and their sites of action remain to be elucidated.

Key words: secretin, secretin-releasing peptide, tetradotoxin, nitric oxide, capsaicin, met-enkephalin, vagotomy
INTRODUCTION

Since the discovery of secretin by Bayliss and Starling in 1902 (1), secretin has been purified, sequenced and its hormonal status has been well established in the last century. Secretin is released mainly from the duodenal mucosa by gastric acid entering the duodenum, although digested products of fat and protein, bile acids and some herbal extracts are shown also to release secretin (2). Acid in the duodenum appeared to be the major stimulant of secretin release. Li et al. (3) has demonstrated that the release of secretin by acid is mediated by a secretin-releasing peptide. Recent studies have provided evidence that the release and action of SRP as well as the physiological actions of secretin are neurally mediated. Several neuropeptides and neurotransmitters appear to mediate neural regulation of the releases and actions of SRP and secretin. In this article we will provide an overview of recent progress in this area.

Neural regulation on release and action of secretin releasing peptide (SRP)

An SRP was found in concentrated duodenal acid perfusate collected from donor rats. When the perfusate was administered intraduodenally to recipient rats,
it stimulated pancreatic exocrine secretion rich in bicarbonate and increased plasma secretin concentration (3), whereas the concentrate of a control saline perfusate was inactive. The active agent in concentrated acid perfusate (CAP) was found to be heat stable and trypsin-sensitive. Thus it is a heat stable polypeptide with an apparent MW of <10,000. The SRP activity was significantly diminished in the CAP obtained from donor rats pretreated with tetrodotoxin, propranolol, vagotomy or perivagal capsaicin but not from the rats pretreated with atropine, hexamethonium; Prop, propranolol. Reproduced from Li et al. (4) with permission.

**Fig. 2.** Effect of various neural blockade, vagotomy or perivagal application of capsaicin in recipient rats on CAP-stimulated secretin release. The abbreviations are: CSP, concentrate of saline perfusate (from upper small intestine); CAP, concentrate of acid perfusate (from upper small intestine); TTX, tetrodotoxin; VT, bilateral vagotomy; CP; perivagal capsaicin; AT, atropine; Hx, hexamethonium; Prop, propranolol. Reproduced from Li et al. (4) with permission.
mediate acid-elicited release of SRP through both 5-HT₂ and 5-HT₃ receptor subtypes, although the underline mechanism is not known at present. In addition, CAP prepared from untreated donors (control) was unable to increase plasma secretin concentration in recipient rats pretreated with tetrodotoxin, vagotomy or perivagal capsaicin but not with atropine, hexamethonium or propranolol (4), indicating that the action of SRP is also neurally mediated depending on a non-cholinergic, non-adrenergic vagal afferent pathway (Fig. 2). Pituitary adenylate cyclase activating polypeptide (PACAP), a neuropeptide, stimulates pancreatic exocrine secretion (7) and inhibits gastric acid secretion (8) in anesthetized rats. In both cases, iv administration of a specific anti-secretin serum inhibited the effect of PACAP, strongly suggesting that the action of PACAP was mediated by the release of secretin. PACAP also stimulates the release of secretin from secretin-producing cells (9). Thus, PACAP is a candidate neuropeptide mediating the release and/or action of SRP.

**Neural regulation on the actions of secretin**

The physiological actions of secretin to stimulate pancreatic exocrine secretion and to inhibit gastric acid secretion and gastric motility are also neurally mediated through the vagal afferent pathway. Thus, in anesthetized rats, perivagal application of capsaicin that ablated the vagal afferent fibers caused inhibition of
pancreatic exocrine secretion stimulated by a physiological dose of secretin (2.5 and 5 pmol/kg/h) but not by a pharmacological dose (10 pmol/kg/h) (Fig. 3). Perivagal capsaicin treatment also prevented inhibition of gastric acid secretion (10) and gastric emptying (11) in rats elicited by a physiological dose but not by a pharmacological dose of secretin. Vagotomy, vagal ligation or perivagal colchicine (but not capsaicin) also reduced secretin binding sites in rat forestomach membranes and caused a right shift in inhibition of contraction of rat forestomach muscle strip (12), suggesting modulation of secretin receptor number in the forestomach through the vagal efferent pathway. However, the neural mechanism involved remains to be investigated. Nevertheless, some candidate neurotransmitters or neuropeptides have been implicated. Except in the rat, secretin-stimulated pancreatic exocrine secretion is profoundly inhibited by atropine, suggesting that the action of secretin is mediated through a muscarinic cholinergic pathway. Fig. 4 provides an example of inhibition of secretin-stimulated pancreatic secretion by atropine in humans (13). In conscious rats, secretin-stimulated pancreatic exocrine secretion was inhibited by a NO synthase inhibitor, N-nitro-L-arginine, and the inhibition was reversed by the substrate of the enzyme, arginine, suggesting that NO mediates the action of secretin (14). Moreover, 5-HT antagonists, ketanserin and ondansetron (Fig. 5) (6), and Met-enkephalin (5) inhibited pancreatic secretion stimulated by physiological doses of secretin. These observations suggest that 5-HT also mediates the action of

![Diagram](image.png)

**Fig. 4.** Effect of atropine on secretin-stimulated pancreatic exocrine secretion in humans. Reproduced from You et al. (13) with permission.
secretin through the 5-HT\textsubscript{2} and 5-HT\textsubscript{3} receptor subtypes, whereas Met-enkephalin is also involved in negative regulation of action of secretin on the exocrine pancreas. In isolated and perfused rat pancreas, electrical field stimulation enhanced stimulation of pancreatic secretion by secretin. The enhanced secretion was reduced by atropine (15) or a specific anti-GRP serum (16) and abolished by combination of atropine and the antiserum (16), suggesting that the enhancement of the effect of secretin was mediated by acetylcholine and GRP released from intrapancreatic neurons. The physiological stimulant of these intrapancreatic neurons is unknown at present. Jo \textit{et al.} (17) has reported that electrical stimulation of medial amygdala in anesthetized rats, though ineffective by itself, enhanced pancreatic exocrine secretion of bicarbonate and fluid stimulated by perfusion of the duodenum with diluted HCl or intravenous administration of a sub-stimulatory dose of porcine secretin. The effect of electrical stimulation of central amygdala was abolished by truncal vagotomy, indicating mediation through the vagus nerve. This observation indicates that signal from central nervous system can modulate the action of secretin on the exocrine pancreas through the vagus. It is not known whether or not the effect is due to the release of CCK-8 from the vagus (18), acetylcholine from pancreatic neurons, or other neurotransmitters or neuropeptides to potentiate the action of secretin.

In summary, the release and actions of secretin is neurally regulated involving both the vagus nerve and intrapancreatic neurons. The actions of secretin also

\begin{figure}
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\includegraphics[width=\textwidth]{secretin_graph.png}
\caption{Effect of 5-HT\textsubscript{2} receptor antagonist, ketanserin and 5-HT\textsubscript{3} receptor antagonist, ondansetron on secretin-stimulated pancreatic exocrine secretion in anesthetized rats. Ketanserin (KT), Ondansetron (ON) or combination of both inhibited pancreatic exocrine secretion stimulated by physiological doses of secretin (5 pmol/kg/h or lower) but had insignificant effect on secretion elicited by a pharmacological dose of secretin (10 pmol/kg/h). Reproduced from Li \textit{et al.} (6) with permission.}
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may be modulated by the central nervous system. The exact neural pathway(s) and the neurotransmitters or neuropeptides involved in these regulatory mechanisms remain to be uncovered.

REFERENCES
